DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021956/S-003

SUPPLEMENT APPROVAL

AstraZeneca LP
Attention: Ian Wogan
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated June 20, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dutoprol (metoprolol succinate extended release and hydrochlorothiazide) 25 / 12.5 mg, 50 / 12.5 mg, 100 / 12.5 mg.

This Prior Approval supplemental new drug application provides for the following labeling revisions consistent with the March 2011 Guidance for Industry "*Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*" in addition to other editorial changes.

The following has been added or ~~deleted~~;

Under **CLINICAL TRIALS**,

> There are no trials of the DUTOPROL combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but both the metoprolol and hydrochlorothiazide components have demonstrated such benefits.

AND

> TABLE 1 has been modified from, ~~TOPROL XL~~ to Metoprolol succinate extended release

Under **INDICATIONS AND USAGE**,

> ~~DUTOPROL is indicated for the management of hypertension. The fixed-dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).~~
>
> DUTOPROL is a combination tablet of metoprolol succinate, a beta adrenoceptor blocking agent and hydrochlorothiazide, a diuretic. DUTOPROL is indicated for the

treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol and hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (eg, on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

DUTOPROL may be administered with other antihypertensive agents.

Under **PRECAUTIONS**,

Metoprolol succinate extended release
Worsening cardiac failure may occur during up-titration of beta blockers. If such symptoms occur, diuretics should be increased and the dose of beta-blocking agent should not be advanced until clinical stability is restored. It may be necessary to lower the dose of DUTOPROL or temporarily discontinue it. (See ~~WARNINGS~~ DOSAGE

AND ADMINISTRATION) Such episodes do not preclude subsequent successful titration of DUTOPROL.

Under **HOW SUPPLIED**,

The NDC numbers have been revised.

AND

Manufactured for: AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: AstraZeneca AB
S-151 85 Södertälje, Sweden

~~Made in Sweden~~

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
12/19/2011